Remarks

Before this Amendment, claims 1-18, 20-23, 27-36, and 46-71 were pending. By this Amendment, claim 3 (and dependent claim 19 therefrom) has been canceled and re-submitted as new claims 72 and 73 so that these dependent claims would depend from a previous claim rather than a later claim. New claims 74-80 have been added. Accordingly, claims 1, 2, 4-18, 20-23, 27-36, and 46-80 are now pending.

The rejections under 35 U.S.C. §112

Claims 1-23 and 46-71

Claims 1-23 and 46-71 were rejected for lack of enablement. The Examiner listed the eight factors from In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) that should be considered when evaluating enablement and concluded that those factors favored a conclusion of lack of enablement.

The Applicants do not agree that consideration of the Wands factors leads to a conclusion of lack of enablement and therefore respectfully traverse this rejection and ask that it be withdrawn. The Applicants address the Wands factors individually below.

The nature of the invention

With respect to this factor, the Examiner merely stated her understanding that the invention is directed to "methods of protecting a female reproductive system against an artificial or natural insult comprising administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (ASMase) gene products." (Office Action, page 3) There was no explanation as to how this characterization of the invention contributes to a conclusion of lack of enablement. Therefore, the Applicants respectfully submit that the Examiner has not shown that this factor favors a conclusion of lack of enablement. [1]

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[1] The PTO has the initial burden of challenging a presumptively correct enabling disclosure. See In re Marzocchi, 439 F.2d 220, 223, 169 USPQ at 370:
"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of

The Applicants believe that practicing the invention is quite straightforward and simply involves the administration of a composition that antagonizes acid sphingomyelinase. The specification teaches that such administration is carried out in a manner similar to the administration of other pharmaceutical compositions (see, e.g., page 17, lines 4-6; page 17, lines 21-23; page 18, lines 1-5; page 19, line 3 to page 20, line 22) and thus presents no special problems in terms of enablement. Thus, this Wands factor favors a conclusion of enablement.

Moreover, as discussed below, there is a common scientific thread running through the various claimed embodiments that ties together the embodiments and assures that the practice of each embodiment will not require undue experimentation.

The state of the prior art

Here, the Examiner merely characterized her view of what the prior art teaches without explaining why those teachings lead to a conclusion of lack of enablement. (Office Action, page 3) Thus, for this factor, too, the Applicants respectfully submit that the Examiner has not shown that this factor favors a conclusion of lack of enablement.

The relative skill of those in the art

The Applicants agree that the level of skill in the art is high, but not only in the art of controlling cell apoptosis. The level of skill is high in the entire field of female reproduction. Those who would practice the invention would ordinarily be physicians, i.e., those having an M.D. degree. This represents a high level of skill and favors a conclusion of enablement.

The predictability or unpredictability of the art

The Examiner did not explain why this factor favored a conclusion of lack of enablement. Instead, the Examiner merely stated the criteria for applying this factor, *viz.*:

> The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results from the claimed invention. The lower the predictability, the higher the direction and guidance that must be provided by Applicant. (Office Action, page 4)

> § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

It is the Applicants position that the predictability of extrapolating the invention from the working example and other teachings of the specification to the entire range of claimed embodiments is high since, as explained below, the same scientific principles relating to apoptosis and its prevention which determined that the working example was a success would be expected to determine that those claimed embodiments would also be successes.

The breadth of the claims

The Examiner stated that the claims are very broad and that no correlation has been established between the various artificial and natural insults for which the invention provides protection.

The Applicants do not agree that no correlation between insults has been provided. Apoptosis of the female reproductive system provides the correlation. Apoptosis plays an important role in the various artificial and natural insults to which the claims are directed and the invention provides methods of inhibiting such apoptosis by the administration of antagonists of acid sphingomyelinase.

As taught by the specification and the prior art, the artificial and natural insults to the female reproductive system exert their deleterious effects in large part by triggering apoptosis. For example, the specification teaches that apoptosis is important in cellular responses to a variety of natural and artificial insults (page 9, lines 7-8). The specification also teaches that: heat insults induce apoptosis (page 15, line 1); oocyte loss through aging occurs via apoptosis (page 15, lines 19-22); apoptosis plays a fundamental role in ovarian health (page 2, lines 2-18; page 3, line 20 to page 4, line 2); and apoptosis can lead to damage to the ovary, which in turn can lead to problems associated with menopause and sterility (page 1, lines 16-18).

The scientific literature supports these statements in the specification.

The scientific literature teaches that chemical insults such as chemotherapy cause damage largely through apoptosis. See, e.g., Gong et al., 1999, Nature 399:806-809[2], abstract: "Cancer chemotherapeutic agents such as cisplatin exert cytotoxic effect by inducing DNA and activating programmed cell death (apoptosis)."

See also Springer et al., 1996, Toxicol. Appl. Pharmacol. 139:394-401[3], which discloses that the chemical insult of treatment with 4-vinylcyclohexene diepoxide (VCD) results in apoptosis of cells in the female reproductive system. See page 394, right column:

> These results demonstrate that the initial evidence of impending destruction of small pre-antral follicles is first consistently visualized following 10 days of daily

[2] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.
[3] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.

> dosing with VCD, although a measurable reduction in oocyte numbers has not yet occurred. Despite the fact that internucleosomal cleavage of genomic DNA was not observed, morphological evaluations support that granulosa cells and oocytes in primordial and primary follicles are destroyed via the induction of apoptosis.

In view of the above evidence, it is clear that, at a minimum, claims 74-78, where the artificial insult is limited to chemotherapeutic drugs, are enabled.

Perez & Tilly, 1997, Human Reproduction 12:2781-2783[4] provided evidence that apoptosis is involved in age-related insults of the female reproductive system that impair oocyte function. In the instances studied, this effect of apoptosis appeared to be mediated through the cumulus cells (CC) that surround the oocyte. See the abstract: "These results demonstrate that the age-dependent acceleration of apoptosis of oocytes maintained in vitro requires the CC."

Other publications also disclose the role of apoptosis in mediating the natural insult of aging in the female reproductive tract and menopause. See Perez et al., 1999, Nature Genetics 21:200-203[5], abstract:

> Female mammals are endowed with a finite number of oocytes at birth, each enclosed by a single layer of somatic (granulosa) cells in a primordial follicle. The fate of most follicles is atretic degeneration, a process that culminates in near exhaustion of the oocyte reserve at approximately the fifth decade of life in women, leading to menopause. Apoptosis has a fundamental role in follicular atresia. [citations omitted]

This age-related degeneration of follicles known as atresia has been attributed to apoptosis in humans. See Kugu et al., 1998, Cell Death and Differentiation 5:67-76[6], at page 67, right column: "We conclude that apoptosis occurs during, and is probably responsible for, follicular atresia in the human and baboon ovary."

In view of this extensive evidence of the role of apoptosis in age-related insults, it is clear that claims directed to age-related insults (e.g., claim 79) are enabled.

The scientific literature teaches that apoptosis is involved in the processes of ovarian development and cyclicity. See Kugu et al., 1998, Cell Death and Differentiation 5:67-76, at page 67, right column:

> Using sensitive biochemical and molecular biological analyses, the occurrence of apoptosis in female germ cell, follicular granulosa cells, and luteal cells during ovarian development and cyclic function in laboratory and domestic animal species has been established.

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[4] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.
[5] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.
[6] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.

In view of this evidence of the role of apoptosis in the processes of ovarian development and cyclicity, it is clear that claims directed to ameliorating the effects of ovarian development and cyclicity (e.g., claims 27-36) are enabled.

The scientific literature teaches that hormonal treatment (e.g., with gonadotropins) act to suppress atresia by inhibiting apoptosis, thus implicitly teaching that hormonal deprivation is a chemical insult that acts through apoptosis. See Flaws et al., 1995, Endocrinol. 136:4351-4359[7], at page 4356, right column:

> Several recent studies have reported the occurrence of apoptosis to be a fundamental mechanism underlying follicular atresia in diverse species and have provided evidence that gonadotropins, as anticipated, function to promote follicular survival by suppressing apoptosis in granulosa cells. [citations omitted]

Flaws et al., 1995, Endocrinol. 136:4351-4359, at page 4351, right column, also teach that the chemical insult of growth factor deprivation (via culture in serum-free conditions) acts through apoptosis (as judged by the characteristic DNA cleavage pattern of apoptotic cells). "Lastly, extensive levels of internucleosomal DNA cleavage were also detected in avian granulosa cells incubated for 6 h under serum-free conditions."

Tilly et al., 1992, Mol. Endocrinol. 6:1942-1950[8] showed that deprivation of growth factors caused by culture under serum-free conditions leads to apoptosis in female reproductive system cells and treatment with the growth factors EGF, TGFα, and bFGF can inhibit such apoptosis. See page 1942, right column:

> Our finding indicate that: 10 both granulosa cells and follicles cultured under serum-free conditions undergo a spontaneous onset of apoptosis; and 2) EGF, TGFα, and bFGF, acting through the tyrosine kinase pathway, are potential physiological inhibitors of apoptotic cell death in the ovary.

See also Johnson et al., 1996, Endocrinol. 137:2059-2066[9], at the paragraph bridging pages 2059-2060:

> Recently, there have been a number of reports implicating gonadotropins, growth factors, or other ovarian-derived factors in the attenuation of apoptosis in incubated rat whole follicles and isolated granulosa cells. ... In all instances reported to date, rat follicles or isolated granulosa cells prepared as described

[7] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.
[8] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.
[9] A copy of this publication is provided with the Supplemental Information Disclosure Statement filed herewith.

> exhibit a significant degree of apoptosis within 24 h of incubation in the absence of supportive hormonal treatment. [citations omitted]

In view of this evidence above with respect to the role of apoptosis in mediating the effects of hormone deprivation and growth factor deprivation, it is clear that claims directed to hormone deprivation and growth factor deprivation (e.g., claim 80) are enabled.

Since apoptosis plays an important role in the various artificial and natural insults recited in the claims and the invention provides a way of inhibiting apoptosis by the use of agents that antagonize acid sphingomyelinase gene products, there is a correlation between the artificial and natural insults such that one can extrapolate from the specifically disclosed embodiments to the entire breadth of the claimed embodiments. Therefore, the breadth of the claims is entirely appropriate and this factor also favors a conclusion of enablement.

The amount of direction or guidance

The Examiner asserted that the amount of direction and guidance provided is limited because: "There is no evidence in the specification that established correlation between the different artificial insults claimed by Applicant ..." (Office Action, page 4)

The Applicants disagree and refer to the discussion above which demonstrates that there is a correlation between the artificial insults recited in the claims. The Applicants believe that, given the correlation between the various artificial insults described above, the amount of direction and guidance provided is more than adequate.

The Examiner referred to an alleged lack of correlation between some of the diseases recited in claims 22 and 23. (Office Action, page 4) The Applicants respectfully submit that this misses the point of the invention. The invention is designed to ameliorate the deleterious effects of the treatments (i.e., the artificial insults) for the recited diseases, not the diseases themselves. Thus, what is relevant is a correlation between the treatments, not the diseases. As explained above, there is such a correlation.

With respect to claims 62-71, the Examiner argued that no correlation had been established between different natural insults. The Applicants do not agree that no correlation with respect to natural insults has been established. Once again, the correlation is provided by apoptosis and the use of the present invention to control apoptosis by the administration of antagonists of acid sphingomyelinase gene products. For example, page 15, lines 19-22, of the specification teaches that oocyte loss though aging (a natural insult) occurs via apoptosis. See also page 15, line 14 to page 16, line 1:

> Natural insults, as defined herein, include damages resulting from physiological, biochemical or developmental processes occurring in a female body. A manifest natural insult is apoptosis due to aging. Natural insults are influenced, for example, by genetic background of the female, environmental affects, or both. The functional life span of female gonads is defined by the size and rate of depletion of the endowment of oocytes enclosed within follicles in the ovaries at birth. This continuous loss of oocytes throughout life, referred to by many as the female biological clock, is driven by a genetic program of cell death that is controlled by physiological and biochemical pathways and players and is conserved from worms to humans (Morita & Tilly (1999) *id.*) This invention, as disclosed herein, demonstrates the effect of antagonizers of *ASMase* gene products in combating normal or pre-mature germ cell depletion in a female mammal. [emphasis added]

See also page 9, lines 6-13:

> Apoptosis is a mechanism by which cells are programmed to die under a wide range of physiological, biochemical and developmental stimuli. Apoptosis is also an important cellular response to a large variety of stress signals, induced by natural or artificial factors. Acid sphingomyelinase *(ASMase)* gene disruption is shown to suppress normal apoptotic deletion of oocytes, leading to ovarian hyperplasia. *Ex vivo*, *ASMase-/-* oocytes or wild-type oocytes treated with an agent, capable of antagonizing one or more *ASMase* gene products, resist developmental and anticancer treatment-induced apoptosis, thereby confirming cell autonomy of the death defect. [emphasis added]

In view of the above, the Applicants submit that this factor favors a conclusion of enablement.

The presence or absence of working examples

The specification provides a working example. Example 10, beginning at page 27, is a working example of the use of the invention to protect the female reproductive system against an artificial insult (radiation). Thus, at a minimum, there is no doubt that the Applicants have enabled the present invention in the context of radiation insults. Moreover, since the specification and the art teach that radiation insults as well as various other insults to the female reproductive tract occur at least in significant part by apoptosis, the teachings of the specification (including the working example) and the prior art enable the skilled artisan to practice the invention in the context of other insults, artificial or natural, where apoptosis plays a significant part, including those recited in the claims. This factor therefore favors a conclusion of enablement.

The quantity of experimentation necessary

For this factor, as for several of the other factors, the Examiner relies on an alleged lack of correlation between the insults recited in the claims in order to arrive at the conclusion that this factor argues against enablement. However, as discussed above, a correlation between the insults exists such that one of skill would have no need to engage in undue experimentation. Therefore, this factor, too, favors a conclusion of enablement.

In summary, when the scientific basis of the invention is understood, when the role of apoptosis and its prevention by the invention is considered, it can be seen that all of the Wands factors favor a conclusion of enablement for claims 1-23 and 46-71. Therefore, it is respectfully requested that this rejection be withdrawn.

Claims 27-36

Claims 27-36 were rejected under 35 U.S.C. §112 because: "The specification does not reasonably provide enablement for 'preserving, enhancing, or reviving' ovarian function or 'preventing or ameliorating' menopausal syndromes." (Office Action, page 5)

The Examiner stated that "There is no known art wherein a certain compound is administered to successfully preserve, enhance or revive a body function or prevent a syndrome before the occurrence of malfunction or disease." (Office Action, page 6). The Applicants do not understand the basis for this statement since it appears that there are many instances of preventive treatments known. For example: vaccines, which prevent disease before its occurrence; drugs to control blood pressure or cholesterol levels, which prevent heart attacks; and vitamins, which "preserve or enhance" body functions. In view of the many known instances of preventive therapies, there is no reason to believe that "The asserted utilities are not believable on their face" as asserted at page 5, lines 16-17, of the Office Action.

In support of this rejection of claims 27-36, the Examiner again cited some of the Wands factors. The Applicants disagree with the Examiner's views with respect to most of these factors. The Applicants' view of these factors follows.

The level of ordinary skill

The Applicants agree with the Examiner that the level of ordinary skill is high and note that this favors a conclusion of enablement.

The predictability or lack thereof in the art

The Examiner stated that "In the instant invention, the predictability is very low" (Office Action, page 6, line 15) but did not give reasons for this assertion. At a minimum, the Applicants submit that the Examiner has not carried her burden of showing that this factor favors a conclusion of lack of enablement. Furthermore, the "preserving, enhancing, or reviving" and "preventing or ameliorating" recited in claims 27-36 refer to the effects of natural and artificial insults. As explained above, there is a correlation which allows for the practice of the invention without undue experimentation with respect to these natural and artificial insults. Therefore, the Applicants believe that this factor favors a conclusion of enablement.

The amount of guidance provided

The Examiner stated that: "[A] high level of direction and guidance must be provided by the Applicant. However, no such guidance is provided and no correlation is present between the experiments in the specification and the claimed utility." (Office Action, page 6)

The Applicants disagree. As explained above, there is a correlation between the utilities claimed in that such utilities are the result of the inhibition of apoptosis caused by the administration of antagonists of sphingomyelinase gene products. The specification teaches this and also provides a working example. This should lead to a finding that the amount of guidance provided is more than adequate.

The quantity of experimentation required

The Examiner stated that: "The quantity of experimentation required to use the methods as claimed in the instant invention, based on Applicant's disclosure, would be [sic, an] undue burden because one of ordinary skill in the art would have to perform a significant amount of experiments and clinical trials." (Office Action, page 6)

With regard to the reference to "a significant amount of experiments," the Applicants note that the Court of Appeals for the Federal Circuit has stated that even a considerable amount of experimentation is acceptable if "it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction, in which the experimentation should proceed." In re Wands, 858 F.2d 731, 733, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). As explained above, the specification's teaching with respect to apoptosis and inhibition of sphingomyelinase gene products provides such a reasonable amount of guidance such that, even if "a significant amount of experiments" must be carried out, such experiments would not represent undue experimentation.

The Applicants also note that there is no requirement that clinical trials be conducted. This is because: "The stage at which an invention in this field [pharmaceutical inventions] becomes useful is well before it is ready to be administered to humans." In re Brana, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995).

In view of the above, the Applicants submit that the Examiner has not met her burden of showing that this factor leads to a conclusion of lack of enablement. Moreover, the teachings of the specification and prior art with respect to apoptosis ensure that the quantity of experimentation needed to practice the invention would not be undue. Thus, this factor favors a conclusion of enablement.

In summary, the Applicants submit that for claims 27-36, as for the claims previously discussed, the Wands factors favor a conclusion of enablement. Therefore, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §103

The Examiner maintained the rejection of claims 1-23, 27-36, and 46-71 over Perez et al., Nat, Med. 3:1228-1232 (1997) ("Perez") in view of U.S. Patent No. 5,712,262 to Spiegel ("Spiegel") and further in view of U.S. Patent No. 5,877,167 to Igarashi et al. ("Igarashi"). (Office Action, pages 7-9)

The Applicants respond by repeating, immediately below, arguments that were made in the Appeal Brief filed February 13, 2003. The Applicants then address comments that the Examiner made in the current Office Action in response to the arguments in the Appeal Brief.

Summary of the Applicants' position

The Applicants submit that the cited references do not make the claims obvious because:

- Perez is directed to the *in vitro* administration of sphingosine-1-phosphate to isolated oocytes to protect against an *in vitro* insult to those isolated oocytes.
- The claims are directed to *in vivo* or *ex vivo* (rather than *in vitro*) administration of agents such as sphingosine-1-phosphate to the female reproductive system (not to isolated oocytes) in order to protect against an insult to the female reproductive system (not to isolated oocytes).
- Perez contains an explicit statement of doubt as to whether Perez's *in vitro* results with isolated oocytes can be successfully extrapolated to methods of treating the female reproductive system as opposed to isolated oocytes.

• Spiegel and Igarashi have absolutely nothing to do with oocytes or female reproductive systems and thus should not be combined with Perez. Even if so combined, Spiegel and Igarashi cannot overcome the statements of doubt in Perez as to treating female reproductive systems since Spiegel and Igarashi have nothing to do with female reproductive systems.

Detailed explanation of the Applicants' position

The cited references

Perez discloses studies in which sphingosine-1-phosphate was administered *in vitro* to isolated oocytes that were also exposed *in vitro* to doxorubicin. See page 1228, left column, second line from bottom, where Perez states that the oocytes that were studied were "harvested [*i.e.*, isolated] from superovulated adult female mice" and "maintained in human tubal fluid medium under standard *in vitro* conditions." See page 1229, Figure 2, and the discussion of Figure 2 in the left column, where Perez states that sphingosine-1-phosphate was administered to the isolated oocytes. Perez did not disclose studies in which sphingosine-1-phosphate was administered either *in vivo* or *ex vivo*. In Perez, the oocytes were never returned to the body, but were merely observed *in vitro*. Moreover, the insult (doxorubicin exposure) to the oocytes that were administered sphingosine1-phosphate occurred *in vitro*.

Spiegel is directed to "methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, ..." (Office Action, page 8, lines 1-2). Speigel disclosed the use of sphingosine-1-phosphate.

Igarashi is directed to "a method of inhibiting tumor cell chemoinvasion." (Office Action, page 8, line 7). Igarashi disclosed the use of sphingosine-1-phosphate.

Spiegel and Igarashi do not discuss oocytes or female reproductive systems.

Differences between the claims and the cited references

The present claims are directed to "methods of protecting [a] female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women" (Office Action, page 7). Since these methods do not encompass treating isolated oocytes *in vitro*, all of these methods require the *in vivo* or *ex vivo* use of compositions (including

sphingosine-1-phosphate) to treat the female reproductive system (as opposed to isolated cells from that system). Moreover, the present claims are directed to treatments that are given in response to insults that occur *in vivo* rather than *in vitro*.

Perez is directed only to the *in vitro* use of sphingsine-1-phosphate (i.e., administered to isolated oocytes) and not its *in vivo* or *ex vivo* use. The use of sphigosine-1-phosphate in Perez is limited to use in conjunction with *in vitro* insults. Spiegel and Igarashi are not directed to treating the female reproductive system in any manner.

Why the rejection should be withdrawn

The cited references do not provide a reasonable expectation of success for the claimed invention

The Applicants contend that Perez, Spiegel, and Igarashi, in any combination, do not provide a reasonable expectation of success for the claimed invention.

It is well settled that a finding of obvious requires that the cited references provide a reasonable expectation of success for the claimed invention. It is not sufficient that the references make it obvious to try to make the claimed invention. See, *e.g.*, In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), where the Federal Circuit said:

> [A] proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). [emphasis added]

Perez alone cannot provide a reasonable expectation of success for the claimed invention because:

- Perez is directed to an *in vitro* method (administering sphingosine-1-phosphate to isolated oocytes) to protect against an *in vitro* insult (administering doxorubicin to isolated oocytes).
- The present claims do not encompass *in vitro* methods to protect against *in vitro* insults.
- Perez contains an explicit statement of doubt as to whether Perez's *in vitro* results with isolated oocytes can be extrapolated to *in vivo* treatment of the female reproductive system as in

the present claims. For example, Perez made it clear that *in vitro* effects are not predictive of *in vivo* successes such as preserving ovarian function. See page 1231, sentence bridging left and right columns:

> Despite the significant advances made by this study in defining the biochemical and genetic pathways involved in oocyte destruction following exposure to anticancer drugs, future long-term studies are required to confirm that inhibiting germ cell apoptosis will preserve ovarian function. [emphasis added]

• Perez also taught that *in vivo* treatments of the female reproductive system (*e.g.*, preserving its fertility) require an effect not just on oocytes, but also on the follicles that support oocytes. See page 1230, lines 6-7: "[F]ertility preservation would require maintenance of the entire follicle and not solely the oocyte." Perez, page 1230, col. 1, lines 6-7. Perez contains no demonstration of the effects of sphingosine-1-phosphate on follicles and thus cannot provide a reasonable expectation of success for treatments that depend on effects on follicles.

The Examiner did not argue that Perez alone provided a reasonable expectation of success. The Examiner instead argued that it was the combination of Spiegel and Igarashi with Perez that provided a reasonable expectation of success. See the Office Action, at page 9, lines 2-5:

> Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful.

In other words, the Examiner is relying on references directed to neurodegenerative aging diseases and the metastasis of tumor cells in order to provide a reasonable expectation of success for an invention directed to the *in vivo* protection of the female reproductive tract! These three types of health problems have no obvious connection and the Examiner has not provided an explanation of why they might be connected. The Applicants do not understand how the lack of reasonable expectation of success in Perez can be negated by two references that are directed to entirely different health problems from those of both Perez and the present claims.

The cited references should not be combined

That the Examiner could not explain how the cited references might provide a reasonable expectation of success is not surprising when one considers the content of the references. Spiegel and Igarashi cannot bridge the gap between Perez's *in vitro* results in oocytes and the Applicants' *in vivo* invention directed to female reproduction because Spiegel and Igarashi have absolutely nothing to do with oocytes or female reproduction.

The Examiner has never contended otherwise. According to the Examiner, Spiegel is directed to "methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, ..." (Office Action, page 8, lines 1-2). Igarashi is directed to "a method of inhibiting tumor cell chemoinvasion." (Office Action, page 8, line 7).

Spiegel and Igarashi are not directed to the field of the Applicants' invention, mammalian female reproduction. Nor are Spiegel and Igarashi directed to the particular problems solved by the present claims: protecting a female reproductive system against an artificial insult (claims 1, 2, 4-18, and 20-23); preserving, enhancing, or reviving ovarian function (claims 27-32); preventing or ameliorating menopausal syndromes (claims 32-36); protecting a female reproductive system from damage caused by treatment for a disease, disorder, or condition (claims 46-61); and protecting a female reproductive system against an natural insult (claims 62-72).

References that are directed neither to the field of the applicant's invention or to the particular problem with which the applicant is concerned may not be used to support an obviousness rejection. See, *e.g.*, In re Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443 (Fed. Cir. 1992):

> In order to rely on a reference as a basis for rejection of the applicant's invention, the reference must either be in the field of the applicant's endeavor, or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.

Since Spiegel and Igarashi are directed neither to the field of the Applicants' invention or to the particular problem with which the Applicants were concerned, Spiegel and Igaraashi should not have been combined with Perez.

The Examiner's responses to the Applicants' arguments

Most of the Examiner's comments with respect to the Applicants' arguments in the Appeal Brief merely re-stated positions the Examiner took elsewhere in the Office Action. However, the Examiner did raise two new points.

The Perez statement of doubt

The Examiner commented that the statement of doubt in Perez "does not imply that SPP cannot be effective in vivo, but rather contemplates the factors required for preserving fertility in vivo." (Office Action, page 9, lines 15-17)

The statement in question is the sentence found at page 1231, bridging the left and right columns. This sentence reads:

> Despite the significant advances made by this study in defining the biochemical and genetic pathways involved in oocyte destruction following exposure to anticancer drugs, future long-term studies are required to confirm that inhibiting germ cell apoptosis will preserve ovarian function. [emphasis added]

In response to the Examiner's comment, the Applicants point out that there is no mention in this sentence of the "factors" that Perez is supposedly contemplating. Neither Perez nor the Examiner state what such "factors" might be. The Examiner has not explained why one should read mention of such undisclosed "factors" into what appears to be a straightforward statement. Perez is simply saying: We have made some advances in understanding what is happening in vitro with respect to isolated oocytes, but further studies are needed to determine whether such advances can be extended to the in vivo milieu of preserving ovarian function.

Moreover, the Examiner seems to be applying the wrong legal standard. The relevant standard is not whether Perez teaches that sphingosine-1-phosphate cannot be effective in vivo. The standard is whether Perez provides a reasonable expectation of success for the use of sphingosine-1-phosphate in vivo. A statement that "future long-term studies are required" seems to the Applicants to be a clear statement that a reasonable expectation of success is lacking.

The field of Spiegel

The Examiner stated that Spiegel is in the same field as the invention because: "Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases,

including aging, which is defined by Applicant as a natural insult." (Office Action, page 10, lines 1-3)

The Applicants do not agree that the specification defines aging in connection with neurodegenerative diseases (as in Spiegel) as a natural insult. Rather, the specification teaches that aging of the female reproductive system is a natural insult. See page 5, lines 8-9: "Natural insults to [sic, the] reproductive system occurs as a consequence of aging, ..."

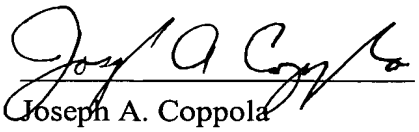
Accordingly, the Applicants maintain their position that Spiegel is not directed to the field of the invention.

In view of the above, the Appellants submit that it has been demonstrated that claims 1-23, 27-36, and 46-71 are not obvious under 35 U.S.C. §103(a) over Perez, Spiegel, and Igarashi and it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for July 9, 2003. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby also make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: September 26, 2003 By: 

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